201-15512

2-METHYL-2-METHYLTHIOPROPANAL OXIME

(ALDICARB OXIME)

CAS Number 1646-75-9

USEPA HPV CHALLENGE PROGRAM SUBMISSION

Submitted by:

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SUBMISSION OVERVIEW AND TESTING PLAN FOR 2-METHYL-2-METHYLTHIOPROPANAL OXIME (ADO)

Aldicarb oxime (ADO) is used as an agricultural intermediate in the production of carbamate pesticides. It is produced by Honeywell International Inc. at its plant in Hopewell Virginia. It is sold to one customer who uses it at only one one site, where ADO is reacted with methyl isocyanate to produce an aldicarb formulation (Aldicarb, Temik). This reaction is believed to occur in a sealed system to prevent exposure to the methyl isocyanate.

ADO is primarily used by industrial workers experienced in the handling of substances of greater toxicity. Significant airborne levels of ADO should not occur due to its low vapor pressure. Honeywell has established PEL of 10 ppm (54.3 mg/$m^{3)}$ as an 8 hour TWA.

ADO is a clear, colorless liquid sold at a purity of >99%. Valid physical-chemical values are available for ADO including melting point, boiling point, vapor pressure, partition coefficient and water solubility.

Environmental releases are limited to fugitive emissions. As ADO is produced and consumed in sealed systems these releases are small.Test data indicate that ADO is stable and soluble in water. ADO's vapor pressure is very low (< 0.1 mm Hg). Therefore, it should not volatilize into the air very quickly and would tend to stay in water. No photodegradation data are available. The results of an acceptable biodegradation study indicate that ADO only slowly biodegrades in soil. No data are available on transport between environmental compartments. The high partition coefficient suggests that ADO has the potential to bioaccumulate.

Acceptable ecotoxicity data are available for rainbow trout (*Salmo gairdneri)*, bluegill sunfish (*Lepomis macrochirus)*, and the invertebrate *Daphnia magna.* Acute LC_{50}/EC_{50} values have been reported as 28 mg/L, 275 mg/L and 343 mg/L, respectively. Based on these values, ADO is considered slightly to moderately toxic to aquatic organisms. Concentrations of 500 mg/L or less of ADO have been reported to have no inhibitory effect on the metabolism of activated sludge microorganisms. No data are available on the effects of ADO on algae.

Sufficient valid mammalian information exists that indicates ADO is only slightly toxic with acute oral exposure and moderately toxic via inhalation. Three acute oral studies in rats using neat ADO report relatively consistent LD_{50s} ranging from 724 to 809 mg/kg. Administration of ADO in corn oil greatly reduces its toxicity most likely due to a reduced rate of absorption from the oil as a consequence of ADO's high solubility in oil as shown by the chemical's high partition coefficient.

Inhalation studies on aerosols of ADO determined a 4- hour LC_{50} of 1.23 mg/L and a 1-hour LC_{50} > 2 mg/L. Acute dermal data that exist indicates ADO is also slightly to moderately toxic by this route although the validity of the available studies is questionable. Toxic effects observed in adequate repeated dosing ADO diet studies of 7 days and 13-weeks were limited to depression of body weights which may have been an indirect effect of ADO as food consumption was reduced in the affected animals. Reproductive organs evaluated microscopically in the 13- week study were not affected by ADO. No data are available on ADO for developmental toxicity.

ADO was negative for mutagenicity with and without metabolic activation in two separate Ames tests. ADO was positive in a mouse lymphoma study without metabolic activation but not with metabolic activation. Data on the potential of ADO to cause chromosome aberrations is not available.

With regard to the HPV program, it is the opinion of the submitter that sufficient and acceptable information on ADO exists for: all of the required **physical-chemical properties**; for the required **environmental fate/transport**, endpoints of water stability, photodegradation, fugacity and biodegradation; for the acute fish and acute invertebrate **ecotoxicity** endpoints; and for the acute oral, acute dermal, acute inhalation, repeated dose, reproductive toxicity (based on reproductive organ evaluation in a subchronic study) and genotoxicity -point mutation **mammalian toxicity** endpoints. No additional testing needs to be performed for these endpoints.

Information for ADO on acute toxicity to algae, and mammalian developmental toxicity is lacking as a result of these studies not being available. It is the intention of the submitter to model or conduct these studies, pending EPA approval, during the calendar year 2004. While information on chromosome aberration potential is also lacking, giving consideration to the limited exposure potential and the fact that ADO was not active in either the Ames assay or mouse lymphoma assay, sponsor does not feel that this data is required. Studies will be conducted according to GLPs and reference applicable OECD guidelines. To assure that animal welfare concerns are appropriately addressed, the studies will be designed to keep animal use to a minimum to the extent possible within acceptable guidelines.

TESTING PLAN IN TABULAR FORMAT

Aldicarb Oxime **CAS no. 1646-75-9**	**Information available**	**OECD study [1]**	**GLP study**	**Other study[1]**	**Estimation Method**	**Acceptable**	**Testing Required**	**comments**
HPV Endpoint								
Physical-Chemical Properties								
Melting Point	**Y**						**N**	
Boiling Point	**Y**						**N**	
Vapor Pressure	**Y**						**N**	
Partition Coefficient	**Y**						**N**	
Water solubility	**Y**						**N**	
Environmental Fate								
Photodegradation	**N**						**N**	
Water Stability	**Y**		**Y**		**N**	**Y**	**N**	
Transport	**Y**						**N**	**Modeled**
Biodegradation	**Y**		**Y**		**N**	**Y**	**N**	
Ecotoxicity								
Acute fish	**Y**		**Y**			**Y**	**N**	
Acute invertebrate	**Y**		**Y**			**Y**	**N**	
Acute algae	**N**						**Y**	
Mammalian Toxicity								
Acute oral	**Y**		**N**			**Y**	**N**	
Acute dermal	**Y**		**N**			**Y**	**N**	
Repeated dose	**Y**		**N**			**Y**	**N**	
Genotoxicity- point mutation	**Y**		**Y**			**Y**	**N**	
Genotoxicity-chromosome aberration	**N**						**N**	**Not active in Ames and mouse lymphoma assays**
Reproductive toxicity	**Y**			**Y**		**Y**	**N**	**No effects on gonadal tissue in 90-day study**
Developmental toxicity	**N**						**Y**	

1. Most studies predate OECG Guidelines and GLPs.

For the following information sections:

*** = an asterisk prior to a subsection number indicates endpoint is a SIDS requirement**

Study reliability based on the 4-point scoring system of Klimisch *et al.* (1997) where:

1= reliable without restrictions

"studies or data…generated according to generally valid and/or internationally accepted guidelines (preferably performed according to GLP) or in which the test parameters documented are based on a specific (national) testing guideline or in which all parameters described are closely related/comparable to a guideline method"

2 = reliable with restrictions

"studies or data…(mostly not performed according to GLP), in which the test parameters documented do not totally comply with the specific testing guideline, but are sufficient to accept the data or in which investigations are described which cannot be subsumed under a testing guideline, but which are nevertheless well documented and scientifically acceptable"

3 = not reliable

"studies or data…in which there were interferences between the measuring system and the test substance or in which organisms/test systems were used which are not relevant in relation to the exposure (e.g., unphysiologic pathways of application) or which were carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for assessment and which is not convincing for an expert judgment ".

4 = not assignable

"studies or data…which do not give sufficient experimental details and which are only listed in short abstracts or secondary literature (books, reviews, etc)."